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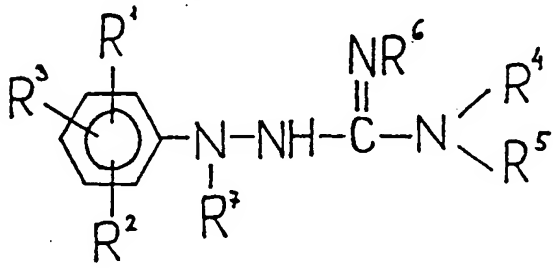
(54) New aminoguandine derivatives and a process for the preparation thereof

(57) New aminoguanidine derivatives of the general formula (I),



(wherein

R^1, R^2 and R^3 each represent hydrogen or halogen atom, C_{1-4} alkyl, nitro, trifluoromethyl or C_{1-4} alkoxy group,

R^4 and R^5 represents a C_{1-4} alkyl group, or NR^4R^5 may form a 5 to 7 membered saturated heterocyclic group containing either one or two nitrogen atoms or a nitrogen and an oxygen atom and being optionally substituted by one or two methyl, hydroxymethyl or hydroxyethyl groups,

R^6 and R^7 each represent a hydrogen atom, normal or branched C_{1-4} alkyl or C_{2-4} alkenyl group, and their pharmaceutically acceptable acid addition salts possess valuable *antiarrhythmic acitivity* and are devoid of the undesired circulatory side effects of known anti-arrhythmic compounds.

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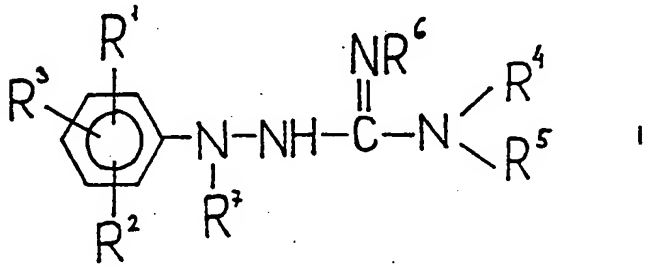
SPECIFICATION

New aminoguanidine derivatives and a process for the preparation thereof

The invention relates to new aminoguanidine derivatives of the general formula (I),



I

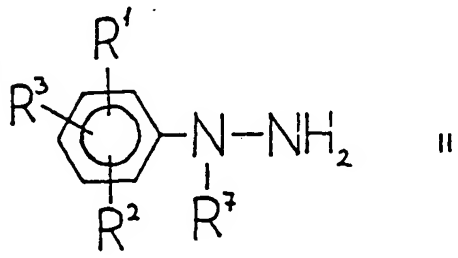
wherein
R^1, R^2 and R^3 each represent hydrogen or halogen atom, C_{1-4} alkyl, nitro, trifluoromethyl or C_{1-4} alkoxy group,
R^4 and R^5 represent a C_{1-4} alkyl group, furthermore NR^4R^5 may form a 5 to 7 membered saturated heterocyclic group containing either one or two nitrogen atoms or a nitrogen and an oxygen atom and being optionally substituted by one or two methyl, hydroxymethyl or hydroxyethyl groups,
R^6 and R^7 each represent hydrogen atom, normal or branched C_{1-4} alkyl or C_{2-4} alkenyl group, and to their pharmaceutically acceptable acid addition salts as well as to a process for the preparation thereof.

Several aminoguanidine derivatives are described in the literature. The 1-aryloxy-alkyl-aminoguanidine derivatives are adrenergic neuron blocking agents (J. Med. Chem. *10*, 391 /1967/), the 1,1-dialkyl-aminoguanidine derivatives are pesticides (published South African patent application No. 69 03,667), while the 1-phenyl-alkyl-aminoguanidines (Neth, patent application No. 6,505,684 and J. Med. Chem. *13*, 1051 /1970/), 4-phenyl-aminoguanidines (published German patent application No. 2,452,691 and U. S. patent No. 4,101,675) and 1-phenyl-4-monoalkyl-aminoguanidines (published South African patent application No. 69 04,823) are antihypertensive agents.

The new compounds of general formula (I) of the invention—the 1-phenyl-4,4-disubstituted-aminoguanidine derivatives—are different in structure from the known 1-phenyl-aminoguanidine derivatives, and affect favourably the rhythmic disorders of the heart, i. e. they are potent antiarrhythmic agents.

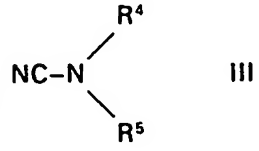
The compounds of general formula (I) are prepared according to the invention either by

a.) reacting a phenylhydrazine derivative of general formula (II)



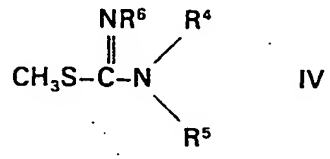
II

wherein R^1, R^2, R^3 and R^7 are defined as above, or its acid addition salt, with either an N,N-disubstituted-cyanamide of general formula (III),



III

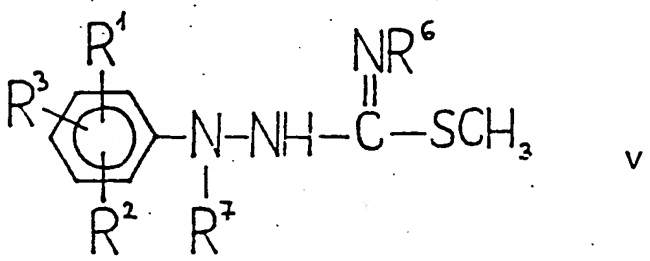
wherein R^4, R^5 or NR^4R^5 are as defined above, or with an isothiourea derivative of general



IV

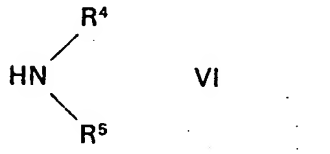
wherein R^4, R^5 or NR^4R^5 and R^6 are defined above or with its acid addition salt; or

b.) reacting an isothiosemicarbazide derivative of general formula (V),



V

wherein R^1, R^2, R^3, R^6 and R^7 are as defined above or its acid addition salt, with a secondary amine of general formula (VI),



VI

wherein R^4, R^5 or NR^4R^5 are as defined above, or with its acid addition salt, and, if desired, the free base of the general formula (I) is liberated from its salt and/or is converted into its acid addition salt by a pharmaceutically acceptable acid.

The tautomers of the above compounds as well as mixtures thereof prepared either by method a.) or b.) are within the scope of the invention.

According to a preferred variant of method a.) of the invention 1.0 M of the phenylhydrazine derivative of general formula (II) or its salt, preferably its hydrohalogenide, is reacted with 1.1 to 1.25 M of the cyanamide derivative of general formula (III), or with 1.0 M of the isothiourea derivative of general formula (IV) or its salt, preferably its hydrohalogenide, in an inert solvent, in a temperature range of 80 to 160°C, preferably at 90 to 130°C, under nitrogen gas. Cyclohexanol, or C_{2-6} normal or branched aliphatic alcohols, i. e. ethanol, n-propanol, i-propanol, n-butanol, amylalcohol or hexylalcohol, are preferred solvents for the reaction. Depending on the solvent and temperature applied the reaction time may amount to 3–72 hours.

According to an other variant of method a.) of the invention the starting materials are melted under nitrogen, preferably at 100 to 130°C. In the reaction of the compounds of general formula (II) and (IV) the starting materials are cautiously melted at 110°C under nitrogen flow, and the melted mixture is stirred for several hours at 130°C. As during the condensation reaction methyl-mercaptan gas is formed, the end of the reaction can be recognised by the end of gas formation. In the reaction of the compounds of general formulas (II) and (III) the progress of the reaction can be monitored by thin-layer chromatography.

According to the preferred method b.) of the invention 1 M of the thiosemicarbazide salt of general formula (V), preferably its hydrobromide or hydroiodide, is reacted with 1 M of a secondary amine of general formula (VI), or 1 M of the thiosemicarbazide of general formula (V) is reacted with a salt of the secondary amine of general formula (VI), preferably its hydrochloride, either in the presence or the absence of a solvent, in a temperature range of 20 to 130°C, for 3 to 72 hours. The solvents applied in variant a.) of the process can preferably be used. The reaction temperature of the reaction in melt, performed in the absence of any solvent, is preferably 110 to 130°C. The end of the reaction can be recognised by the end of methyl-mercaptan gas formation.

In the reaction, performed in a solvent according to either of the process variants, the product formed precipitates in most of the cases from the reaction mixture upon cooling, and can be separated by filtration. In those cases where the product formed fails to precipitate from the solution upon cooling, its precipitation can be induced by the addition of hexane, ether or acetone. In the reactions carried out in melt the cooled melt is dissolved in ethanol, the insoluble part is filtered, and the product is precipitated from the filtrate by the addition of

hexane, ether or acetone. The raw product is purified similarly.

If the acid addition salt of the starting material is applied, in the reaction the acid addition salt of the target product is formed. The base can be set free therefrom with an inorganic or organic base, preferably with solid sodium hydrocarbonate or aqueous triethylamine. If desired, the base can be converted into various other acid addition salts with a suitable organic or inorganic acid.

The starting materials of general formulas (II), (III), (IV), (V) and (VI) as well as the processes for their preparation are known from the literature [J. Am. Chem. Soc. *81*, 4678 (1959); American Chem. J. *42*, 23, Zeitschrift für Elektrochemie *22*, 342; J. Am. Chem. Soc. *72*, 4699 (1950)].

In the process of the invention the following starting phenylhydrazines of general formula (II) or their salts are preferably used: phenylhydrazine, 2-methyl-, 4-methyl-, 2-chloro-, 3-chloro-, 4-chloro-, 2-trifluoromethyl-, 3-trifluoromethyl-, 2-methoxy-, 2,3-dimethyl-, 2,4-dimethyl-, 2,5-dimethyl-, 2,6-dimethyl-, 2-methyl-6-ethyl-, 2,4,6-trimethyl-, 2-methyl-3-chloro-, 2-methyl-4-chloro-, 2-methyl-6-chloro-, 2,5-dichloro-, 2,6-dichloro-, 2-methoxy-, 3,4-dimethoxy-, and 4-nitro-phenylhydrazine as well as α-methyl-, α-i-propyl- and α-allyl-phenylhydrazine.

In the process of the invention the following N,N-disubstituted-cyanamides of general formula (III) are preferably applied as starting materials: dimethyl-cyanamide, diethyl-cyanamide, 1-cyano-pyrrolidine, 1-cyano-piperidine, 1-cyano-2-methyl-, 1-cyano-3-methyl-piperidine, 4-cyano-1-methyl-, 4-cyano-2,6-dimethyl-, 4-cyano-1-(2-hydroxyethyl)-piperazine, 4-cyano-, 4-cyano-2-methyl-, 4-cyano-2,6-dimethyl-morpholine and 1-cyano-hexahydro-azepine.

The following S-methyl-isothioureas of general formula (IV) and their salts can preferably be used as starting materials: N,N,S-trimethyl-isothiourea, N,N-di-ethyl-S-methyl-isothiourea, N,N-tetramethylene-S-methyl-isothiourea, N,N-pentamethylene-S-methyl-isothiourea, N,N,N',S-tetramethyl-isothiourea and N,N-diethyl-N',S-dimethyl-isothiourea.

The following isothiosemicarbazide derivatives of general formula (V) and their salts can preferably be used as starting materials: 2-methyl-phenyl-S-methyl-, 2-chloro-phenyl-S-methyl-, 3-chloro-phenyl-S-methyl-, 2,6-dichloro-phenyl-S-methyl-, 2,6-dimethyl-phenyl-S-methyl-, 2-methyl-phenyl-N,S-dimethyl-, 2-chloro-phenyl-N,S-dimethyl-, 2,6-dimethyl-phenyl-N,S-dimethyl-, 2,6-dichloro-phenyl-N,S-dimethyl-isothiosemicarbazide.

The following secondary amines of general formula (VI) and their salts can preferably be used as starting materials: dimethylamine, diethylamine, pyrrolidine, piperidine, 2-methyl-, 3-methyl-piperidine, N-methyl-, 2,6-dimethyl-, N-(2-hydroxyethyl)-piperazine, morpholine, 2-methyl-, 2,6-dimethyl-morpholine, hexamethyleneimine.

The 1-phenyl-aminoguanidine derivatives of general formula (I) exhibit high antiarrhythmic activity in mouse, cat guinea pig and dog tests. In several tests, in doses of 10–50–100 mg/kg, this antiarrhythmic effect is significant and stable both at parenteral and oral administration.

The antiarrhythmic activity was tested by the following methods:

1. *Aconitin-induced arrhytmia in mice*

Arrhytmia was induced in male mice, weighing 20 to 25 g, by treating them continuously, at a rate of 0.2 ml/min with an infusion containing 5 μg/kg of aconitin. The test compound was administered to the animals either intraperitoneally (by injecting it into the abdominal cavity) 15 minutes before the start of the infusion, or orally 60 minutes before the onset of the infusion. The time of the appearance of arrhythmia was recorded, and the percentage of delay was calculated in relation to the data obtained in the controls, pretreated with 0.9 percent sodium chloride solution only [B. Vargaftig and J.L. Coignet: European J. of Pharmacol. *6*, 49 to 55 (1969); N.K. Dadkar and B.K. Bhattachariya: Arch. Int. Pharmacodyn. *212*, 297 to 301 (1974); D.U. Nwagwu, T.L. Holcslaw and S.J. Stohs: Arch. Int. Pharmacodyn. *229*, 219 to 226 (1977)].

The results are presented in Tables 1 and 2. 1-(2,6-Dimethylphenoxy)-2-aminopropane hydrochloride (Mexiletin) and/or quinidine were applied as reference substances. The acute toxicity values (LD_{50}) were calculated according to the method of Litchfield and Wilcoxon [J. Pharmacol. Exp. Ther., *96*, 99 to 113 (1949)].

Table 1

Examination of the antiarrhythmic effect in anesthesized mice treated with aconitin, with intraperitoneal administration of the test compounds

Compound Example No.	Dose mg/kg i.p.	Delay in the appearance time of arrhythmia %	Number of animals n	LD_{50} mg/kg i. p.
1	25	+164	18	81
	50	+174	18	

Table 1 (continued)

2	25	+79	16	73
	50	+156	16	
3	10	+108	12	
	20	+68*	12	
4	5	+28	5	
	10	+77*	9	
5	25	+113	20	130
	50	+155	20	
6	50	+114	6	
7	25	+50	10	
	50	+128	20	
8	5	+32	6	
	10	+110*	7	
9	50	+171	12	
15	50	+67	6	
21	25	+110	6	
	50	+86**	9	
22	50	+100	20	

* compound is toxic in higher doses

** compound is toxic in higher doses and induces bradycardia

Table 1 (continued)

Reference substance: 1-(2,6-dimethyl-phenoxy)-2-amino-propane.HCl (Mexiletin)	5	+3.5	20	114
	10	+7.7	20	
	25	+33	20	
	50	+83	20	
	75	+162	16	

Table 2

Examination of the antiarrhythmic effect in anesthesized mice treated with aconitin, with oral administration of the test compounds

Compound Example No.	Dose mg/kg p. o.	Delay in the appearance time of arrhytmia %	Number of animals n	LD_{50} mg/kg p. o.
1	50	+102	5	203
	100	+197	14	
2	25	+39	15	220
	50	+71	5	
	100	+150	5	

Table 2 (continued)

5	100	+111	20	400
6	100	+70	6	
7	50	+54	6	
	100	+137	8	
18	100	+74	6	
Reference substance: Mexiletin	100	+93	20	390

2. *Determination of the fibrillation threshold in anaesthesized cats*

The chests of the cats were opened under chloralose-urethane anaesthesia, a bipolar stimulating electrode was fixed onto the heart, and the heart was stimulated electrically with a frequency of 20 Hz, under continuously increasing current strength, until a fibrillo-flattern could be observed. This current strength was considered as the fibrillation threshold of the animal. Thereafter the test compounds were administered, and the increase in the fibrillation threshold value was recorded at i. v. and intraduodenal (i. d.) administration (Szekeres and Papp: Experimental Cardiac Arrhythmias and Antiarrhythmic Drugs, Academic Press, Budapest, 1971).

The values measured are presented in Tables 3 and 4.

Table 3

Effect of the test compounds on the fibrillation threshold measured in anesthesized cat at i.v. administration

Compound Example No.	Dose mg/kg i. v.	Percentage change in the fibrillation threshold following treatment		
		2 min	10 min	20 min
5	0.5	+18.75	+40.75	+37.6
	1.0	+35.2	+55.2	+48.4
	2.0	+101.1	+93.0	+94.15
	4.0	+153.3	+125.65	+124.0
	8.0	+392.8	+354.5	+310.25
11	2.0	+130.6	+149.0	+163.3
	4.0	+176.0	+328.0	+316.0
Mexiletin	10.0	-	+161.2	+92.0

Table 4

Effect of the test compounds on the fibrillation threshold measured in anaesthesized cats at i. d. administration

Compound Example No.	Dose mg/kg i. d.	No. of animals n	Percentage change in the fibrillation threshold 10 minutes following treatment									
			10	20	30	40	50	60	70	80	90	100
5	20	7	+22.2	+29.0	+94.0	+103.7	+100.4	+105.8	+100.3	+121.5	+132.8	+132.3
11	20	4	+5.8	+22.0	+43.8	+79.6	+115	+118	+141	+198	+209.5	+272.5
Quinidine	10	5	+0.4	+26.7	+58.5	+48.5	+32.1	+20.8	+9.5	+8.8	+3.8	0.0

3. *Electrophysiological tests performed in the isolated rabbit heart*

Hearts of rabbits of both sexes, weighing 1 to 2 kg, were removed, the right and left auricles and a segment of the right ventricle were prepared and placed into a vessel filled with nutrient solution. Bipolar platinum electrodes (a stimulating electrode and a lead electrode) were placed on the organ strips, and the electric stimulus threshold and the speed of impulse conduction were measured. The effective refractory period was determined on the basis of the maximal driving frequency. The results were read from the screen of an oscilloscope (Szekeres and Papp: Experimental Cardiac Arrhythmias; Academic Press, Budapest, 1971).

The electrophysiological activities of the compounds of the invention are demonstrated on the example of 1-(2-methylphenyl)-4,4-dimethyl-aminoguanidine hydrochloride (Example 1). The test results are presented in Table 5.

The Table shows that the conduction time in both the left auricle and the right ventricle is prolonged dose-dependently by the compound of the invention, which means a reduction of the speed of impulse conduction. It decreases the maximal driving frequency, indicating a prolongation of the refractory period. The auricular contractility is dose dependently, though moderately reduced by the compound.

Table 5. Electrophysiological effect in the isolated rabbit heart

Test parameters	Compound Example No.	0.25 mg/l	0.5 mg/l	1.0 mg/l	2.0 mg/l	4.0 mg/l	8.0 mg/l
		Percentage dose responses measured in the right ventricle n = 4					
Change in conduction time	1	+0.2	+3.31	+14.84	+36.75	+52.45	+77.82
	Mexiletin				+11		
Change in electric stimulus threshold	1	0	-1.43	+5.42	+20.6	+23.6	+35.8
	Mexiletin				+6		
Change in max. driving frequency	1	-0.88	-0.38	-1.82	-10.33	-17.43	-36.8
	Mexiletin				-28		
		Percentage dose responses measured in the left auricle n = 4					
Change in conduction time	1	+0.54	+8.66	+12.55	+28.42	+47.87	+114.03
	Mexiletin				+24		

Table 5 (continued)

Change in electric stimulus threshold	1 Mexiletin	0	-1.82	-11.8	+30.84 36	+43.4	+83.9
Change in max. driving frequency	1 Mexiletin	-0.08	-0.98	-9.21	-17.09 -32	-28.82	-59.1
Contractility	1	-2.61	-7.57	-15.5	-18.12	-27.08	-37.92

It appears from the above tables that the compounds of the invention are similar or occasionally even superior in antiarrhythmic activity to the presently applied 1-(2,6-dimethylphenoxy)-2-amino-propane hydrochloride (Mexiletin). As an additional advantage, the compounds are devoid of the undesirable circulatory side effects, generally appearing upon the administration of the known antiarrhythmic agents, i. e. they fail to induce a pressure drop in the systemic circulation and a pressure increase in the pulmonary circulation in animals with intact chest or in unanaesthesized, permanently cannulated animals, at a dose range of 0.5 to 4.0 mg/kg. The antiarrhythmic effect of the compounds is not accompanied by any other activity affecting the vegetative nervous system, i. e. the compounds have neither alpha- nor beta-adrenergic blocking, nor adrenergic neurone blocking or parasympatholytic activity.

In addition, the compounds possess significant cardioprotective potency, i.e. their antiarrhythmic activity is also exhibited in the ischemic heart. This cardioprotective effect is three times higher than that of diethylamino-acet-(2,6-dimethyl)-anilide (Lidocain).

The compounds of the invention can be converted to pharmaceutical preparations by methods known in the art by applying additives, carriers and vehicles generally used in drug manufacturing.

A daily dose of 75 mg is planned for the treatment of human subjects weighing about 70 kg.

The following Examples are illustrating but not limiting the scope of the invention.

Example 1

1-(2-Methylphenyl)-4,4-dimethyl-aminoguanidine hydrochloride

Method a.)

A mixture of 1.59 g (0.01 M) of 2-methyl-phenylhydrazine hydrochloride, 3 ml of anhydrous n-propanol and 1 ml (0.0125 M) of dimethyl-cyanamide is heated at 130°C for 5 hours at continuous stirring and under nitrogen gas flow. To the resulting solution which is cooled to 0°C, 15 ml of hexane are added portion-wise. The precipitated white product is filtered on a glass filter, washed with a 4:1 mixture of hexane-ethanol and is dried. Yield 1.45 g (63.4 percent) of the product, m. p. 219 to 221°C.

Method b.)

The procedure described under Method a.) is applied except that n-butanol is used as solvent. Yield 1.33 g (58.2 percent) of the product, m. p. 219 to 221°C.

Method c.)

The procedure described under Method a.) is applied except that cyclohexanol is used as solvent. Yield 1.37 g (60.1 percent) of the product, m. p. 219 to 221°C.

Method d.)

The procedure described under Method a.) is applied except that the reaction is carried out without solvent, at 110°C in a melted form. The resulting melt is suspended in a 4:1 mixture of hexane-ethanol, then it is filtered and dried. Yield 1.28 g (55.9 percent) of the product, m. p. 219 to 221°C.

Example 2

1-(2,6-Dichlorophenyl)-4,4-dimethyl-aminoguanidine

The solution of 3.54 g (0.02 M) of 2,6-dichlorophenylhydrazine, 6 ml of anhydrous n-propanol and 1.56 g (0.022 M) of dimethyl-cyanamide is heated at 130°C for 5 hours at continuous stirring and under nitrogen gas flow. The resulting solution is cooled to 0°C, then 60 ml of hexane are added portion-wise. The precipitated beige coloured product is filtered on a glass filter, it is washed with a 9:1 mixture of hexane-ethanol, and then dried. Yield 3.20 g (64.8 percent) of 1-(2,6-dichlorophenyl)-4,4-dimethyl-aminoguanidine, m. p. 153 to 154°C.

Preparation of the hydrochloride salt

The above base is dissolved in 10 ml of ethanol, then 10 ml of a saturated hydrochloric acid solution in ethanol are added to it dropwise at room temperature and at stirring. The resulting suspension is heated to 70°C and it is stirred at this temperature for 30 minutes. The yellow solution is cooled to 40°C and 80 ml of hexane are added to it at continuous stirring. The precipitated white product is filtered on a glass filter after cooling to 0°C, then it is washed with a 4:1 mixture of hexane-ethanol and dried. Yield 3.59 g (61.5 percent), m. p. 255 to 257°C.

Example 3

1-(2-Chlorophenyl)-4,4-diethyl-aminoguanidine hydrochloride

nitrogen flow. The melt is stirred for 1 hour at 110°C and for 2 hours at 130°C. During the reaction methyl-mercapton gas is liberated. When the gas formation has stopped, the dark red melt is cooled to room temperature, the solidified mass is dissolved in 15 ml of water, the solution is cooled to 0°C, the pH of this solution is adjusted to 8–9 with solid sodium hydrogen-carbonate, then the precipitated beige-coloured crystals are filtered on a glass filter and washed with water having a temperature of 0°C. This wet product on the filter is dissolved in 25 ml of N hydrochloric acid at room temperature, the solution is decoburized with active carbon, then the solution is evaporated to dryness under reduced pressure. The evaporation residue is dissolved in 12 ml of anhydrous, hot ethanol, then it is cooled to 40 to 50°C, and portion-wise 50 ml of hexane are added to it. The precipitated white, crystalline plates are cooled to 0°C, filtered on a glass filter, washed with a 4:1 mixture of hexane and ethanol and dried. Yield 2.55 g (38.5 percent), m. p. 191.5 to 192.5°C.

Example 4

1-(2-Methyl-phenyl)-4,4-diethyl-aminoguanidine hydrochloride

0.73 g (0.01 M) of freshly distilled diethylamine is added to a solution of 3.23 g (0.01 M) of 1-(2-methyl-phenyl)-3-(S-methyl)-isothiosemicarbazide hydroiodide in 10 ml of ethanol, and the solution is stirred at 40°C for 72 hours. During the reaction methylmercaptan is generated. By the end of the reaction the solvent is evaporated at reduced pressure, the residue is dissolved in 10 ml of water, the solution is cooled to 0°C and its pH is adjusted to 8–9 with solid sodium hydrogen carbonate. The precipitated beige-coloured product is filtered on a glass filter and washed with water having a temperature of 0°C. This wet material on the filter is dissolved in 13 ml of N hydrochloric acid at room temperature, the solution is decolourized with active carbon, and evaporated at reduced pressure to dryness. The evaporation residue is dissolved in a hot mixture of 10 ml of acetone and 2 ml of ethanol, the turbid solution is filtered, the filtrate is cooled to room temperature and 25 ml of ether are added to it. The precipitated, beige-coloured crystals are filtered on a glass filter following cooling to 0°C, washed with a 3:1 mixture of ether-acetone, and dried. Yield 0.95 g (37 percent), m. p. 174 to 176°C.

Examples 5 to 54

The compounds presented in *Table 6* can be prepared according to the procedures described in Examples 1 to 4. The Table lists the m. p. and the yield of the compounds, too.

Table 6

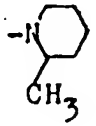
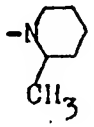
Example No	R^1	R^2	R^3	$N\begin{smallmatrix}R^4\\R^5\end{smallmatrix}$	R^6	R^7	Yield %	Hydrochloride M. p. °C
5	2-CH_3	6-CH_3	H	$N(CH_3)_2$	H	H	61	258-260
6	2-Cl	H	H	$N(CH_3)_2$	H	H	69	252-253
7	2-CH_3	H	H		H	H	47	258-260
8	2-Cl	H	H		H	H	45	212-213
9	H	H	3-Cl	$N(CH_3)_2$	H	H	39	171-174
10	2-CH_3	6-CH_3	H	$N(C_2H_5)_2$	H	H	42	212 -215
11	2-CH_3	6-CH_3	H		H	H	44	272-275
12	2-CH_3	6-CH_3	H		H	H	23	233-237
13	2-CF_3	H	H	$N(CH_3)_2$	H	H	71	238-242

Table 6 (continued)

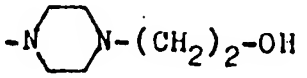
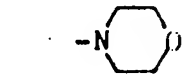
Example No.	R^1	R^2	R^3	$N\begin{smallmatrix}R^4\\R^5\end{smallmatrix}$	R^6	R^7	Yield %	Hydrochloride M. p. °C
14	2-CF_3	H	H	$N(C_2H_5)_2$	H	H	60	202-206
15	2-Cl	2-Cl	H	$N(CH_3)_2$	H	H	63	257-258
16	2-CH_3	6-Cl	H	$N(CH_3)_2$	H	H	40	256-258
17	2-CH_3	H	3-CH_3	$N(CH_3)_2$	H	H	42	239-242
18	H	H	H	$N(CH_3)_2$	H	H	36	162-164
19	H	H	4-Cl	$N(CH_3)_2$	H	H	58	192-200
20	2-CH_3	H	H		H	H	75	245-247
21	2-CH_3	6-C_2H_5	H	$N(CH_3)_2$	H	H	53	253-256
22	2-CH_3	H	H		H	H	51	160-163

Table 6 (continued)

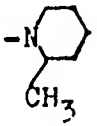
Example No.	R^1	R^2	R^3	$N\begin{smallmatrix}R^4\\R^5\end{smallmatrix}$	R^6	R^7	Yield %	Hydrochloride M. p. °C
23	2-CH_3	H	H		H	H	39	204-205
24	2-CH_3	H	3-Cl	$N(CH_3)_2$	H	H	50	260-264
25	2-CH_3	6-CH_3	4-CH_3	$N(CH_3)_2$	H	H	16	248-251
26	H	5-CH_3O	4-CH_3O		H	H	31	206-207
27	H	H	4-NO_2	$N(CH_3)_2$	H	H	68	258-260
28	2-CH_3O	H	H	$N(CH_3)_2$	H	H	39	95-97
29	2-CH_3	5-CH_3	H	$N(CH_3)_2$	H	H	41	238-240
30	2-CH_3	H	4-CH_3	$N(CH_3)_2$	H	H	52	219-222
31	H	H	4-CH_3	$N(CH_3)_2$	H	H	12	176-179

Table 6 (continued)

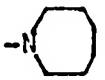
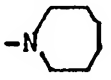
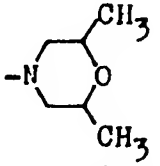
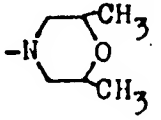
Example No.	R^1	R^2	R^3	$N\begin{smallmatrix}R^4\\R^5\end{smallmatrix}$	R^6	R^7	Yield %	Hydrochloride M. p. °C
32	H	H	H	$N(CH_3)_2$	H	CH_3	46	196-200
33	H	H	H	$N(CH_3)_2$	H	i-propyl	58	95-105
34	H	H	H	$N(CH_3)_2$	H	allyl	41	161-163
35	2-CH_3	H	4-Cl	$N(CH_3)_2$	H	H	45	252-256
36	2-CH_3	6-CH_3	H		H	H	26	260-265
37	2-CH_3	H	H		H	H	35	195-198
38	2-CH_3	6-CH_3	H		H	H	40	276-281
39	2-CH_3	H	H		H	H	54	236-240
40	H	H	H	$N(C_2H_5)_2$	H	CH_3	32	198-200

Table 6 (continued)

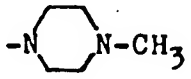
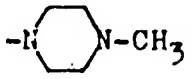
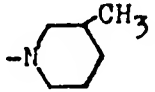
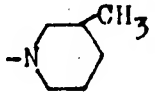
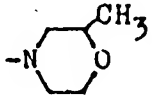
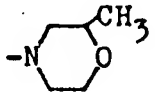
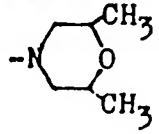
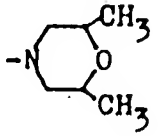
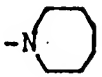
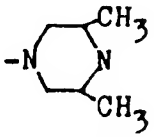
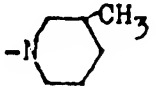
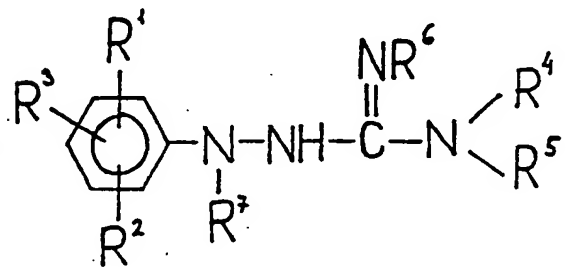
Example No.	R^1	R^2	R^3	NR^4R^5	R^6	R^7	Yield %	Hydrochloride M. p. °C
41	2-CH_3	6-CH_3	H		H	H	52	229-231
42	2-CH_3	6-CH_3	H		H	H	54	205-211
43	2-CH_3	H	H		H	H	12	196-198
44	2-CH_3	6-CH_3	H		H	H	24	216-219
45	2-CH_3	H	H		H	H	10	201-205
46	2-CH_3	6-CH_3	H		H	H	12	209-211
47	2-CH_3	H	H		H	H	28	198-204
48	3-Cl	H	H		H	H	28	222-226

Table 6 (continued)

Example No.	R^1	R^2	R^3	$N(R^4)(R^5)$	R^6	R^7	Yield %	Hydrochloride M. p. °C
49	3-Cl	H	H		H	H	27	228-230
50	2-Cl	H	H		H	H	41	257-259
51	2-Cl	H	H		H	H	42	219-221
52	2-Cl	6-Cl	H		H	H	39	277-279
53	2-CH_3	6-CH_3	H		H-	H	18	286-287 dihydroxide
54	2-Cl	H	H		H	H	35	224-226

CLAIMS

1. Aminoguanidine derivatives of the general formula (I),



wherein

R^1, R^2 and R^3 each represent hydrogen or halogen atom, C_{1-4} alkyl, nitro, trifluoromethyl or C_{1-4} alkoxy group,

R^4 and R^5 represent a C_{1-4} alkyl group, furthermore NR^4R^5 may form a 5 to 7 membered saturated heterocyclic group containing either one or two nitrogen atoms or a nitrogen and an oxygen atom and being optionally substituted by one or two methyl, hydroxymethyl or hydroxyethyl groups,

R^6 and R^7 each represent hydrogen atom, normal or branched C_{1-4} alkyl or C_{2-4}-alkenyl group, and the pharmaceutically acceptable acid addition salts thereof.

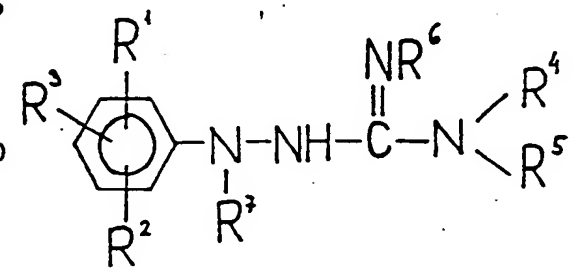
2. 1-(2-Methyl-phenyl)-4,4-dimethyl-aminoguanidine hydrochloride.

3. 1-(2,6-Dichlorophenyl)-4,4-dimethyl-aminoguanidine hydrochloride.

4. 1-(2,6-Dimethyl-phenyl)-4,4-dimethyl-aminoguanidine hydrochloride.

5. Pharmaceutical compositions having antiarrhythmic activity containing as active ingredient at least one compound of the general formula (I), wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have a meaning as claimed in claim 1, and a conventional inert, non-toxic, solid or liquid carrier and/or additive.

6. A process for the preparation of new aminoguanidine derivatives of the general formula (I),



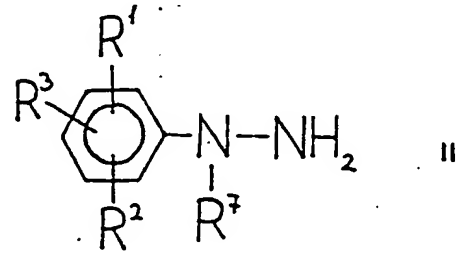
wherein

R^1, R^2 and R^3 each represent hydrogen or halogen atom, C_{1-4} alkyl, nitro, trifluoromethyl or C_{1-4} alkoxy group,

R^4 and R^5 represent a C_{1-4} alkyl group; furthermore NR^4R^5 may form a 5 to 7 membered saturated heterocyclic group containing either one or two nitrogen atoms or a nitrogen and an oxygen atom and being optionally substituted by one or two methyl, hydroxymethyl or hydroxyethyl groups.

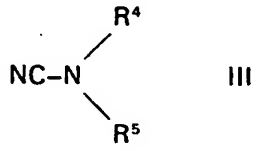
R^6 and R^7 each represent a hydrogen atom, normal or branched C_{1-4} alkyl or C_{2-4} alkenyl group, and pharmaceutically acceptable acid addition salts thereof, characterized by

a.) reacting a phenylhydrazine derivative of general formula (II),



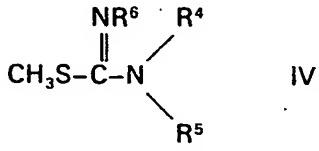
II

wherein R^1, R^2, R^3 and R^7 are as defined above, or its acid accition salt, with either an N,N-disubstituted-cyanamide of general formula (III),



III

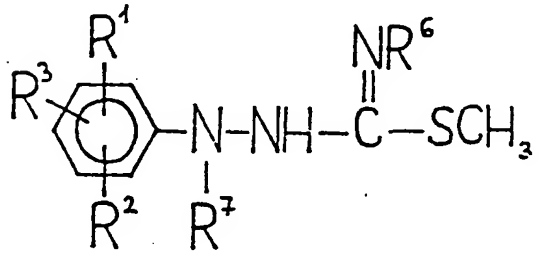
wherein R^4, R^5 or NR^4R^5 are defined as above, or with an isothiourea derivative of general formula (IV),



IV

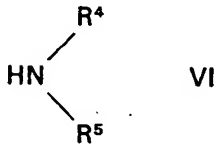
wherein R^4, R^5 or NR^4R^5 and R^6 are as defined above, or with its acid addition salt,
or

b.) by reacting either an isothiosemicarbazide derivative of general formula (V),



V

wherein R^1, R^2, R^3, R^6 and R^7 are as defined above, or its acid addition salt with a secondary amine of general formula (VI),



VI

wherein R^4, R^5 or NR^4R^5 are as defined above, or with its acid additon salt,
and, if desired, the free base of the general formula (I) is liberated from its salt obtained by process variant a.) or b.) and/or is converted into its acid addition salt by a pharmaceutically acceptable acid.

7. A process for the preparation of pharmaceutical compositions having mainly antiarrhythmic activity characterized by transforming one or more compounds of general formula (I)—wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1—or its pharmaceutically acceptable acid addition salts together with carriers, additives or vehicles generally used in drug manufacturing, by methods known in the art, into pharmaceutical compositions.

8. A compound as claimed in claim 1 as hereinbefore described in any one of Examples 1 to 54 or an acid addition salt thereof.

9. A process as claimed in claim 6 substantially as hereinbefore described in any one of Examples 1 to 4 or, by analogy, in any one of Examples 5 to 54.

10. A compound produced by a process as claimed in claim 6 or claim 9.

11. A pharmaceutical preparation comprising a compound as claimed in claim 8 or claim 10 together with one or more inert pharmaceutically acceptable carrier, solvent and/or adjuvant.

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